AMENDMENTS TO THE SPECIFICATION

Replace the paragraph beginning at page 1, line 4 with:

This application claims the benefit of U.S. Provisional Application No. 60/542,311 filed Feb. 6, 2004, the entire contents of which are hereby incorporated by reference herein. This application represents the U.S. national phase entry of PCT/US05/03907, filed Feb. 7, 2005.

Replace the paragraph beginning at page 1, line 32 with:

Preferably, the soluble, CD2-binding LFA-3 polypeptide is an LFA-3 fusion protein, e.g., an LFA-3/immunoglobulin (Ig) fusion protein. An exemplary LFA-3/Ig fusion protein includes a soluble, CD2 binding LFA-3 polypeptide fused to all or part of an Fc region of an IgG, e.g., fused to all or part of an IgG heavy chain hinge region and all or part of a heavy chain constant region. In a preferred embodiment, the Ig fusion protein consists of the amino terminal 92 amino acids of mature LFA-3, the C-terminal 10 amino acids of a human IgG1 hinge region, a CH2 region of a human IgG1 heavy chain, and all or at least part of a CH3 region of a human IgG1 heavy chain. One such fusion protein is AMEVIVE (alefacept). AMEVIVE (alefacept) is encoded by an insert contained in plasmid pSAB152, deposited with American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209 under the accession number ATCC 68720 on October 1, 1991. AMEVIVE (alefacept) is described in more detail herein below.

Replace the paragraph beginning at page 4, line 15 with:

Figure 2 is a bar graph of the percentage of psoriasis patients achieving PASI 50 at two or twelve weeks after treatment for cycles A-D of a multiple course of treatment with AMEVIVE (alefacept).

Replace the paragraph beginning at page 4, line 18 with:

Figure 3 is a graph of the benefit and repeat response in a multiple course of treatment with AMEVIVE (alefacept) for psoriasis.

Replace the paragraph beginning at page 4, line 20 with:

Figure 4 is a bar graph of the maximum length of response time in four psoriasis patients receiving a multiple course of treatment with AMEVIVE (alefacept).

Replace the paragraph beginning at page 4, line 22 with:

Figure 5 is a graph of the mean CD4+ T-cell counts for patients having a multiple course of treatment with AMEVIVE (alefacept).

Replace the paragraph beginning at page 4, line 24 with:

Figure 6A is a graph of the percentage of patients achieving PASI 75 at any time during a multiple course of intravenous (IV) treatment with AMEVIVE (alefacept). FIG. 6B is a graph of the percentage of patients achieving PASI 50 at any time during a multiple course of IV treatment with AMEVIVE (alefacept).

Replace the paragraph beginning at page 4, line 28 with:

Figure 7A is a graph of the percentage of patients achieving a PGA of "clear" or "almost clear" responses at any time during a multiple course of IV treatment with AMEVIVE (alefacept). FIG. 7B is a graph of the percentage of patients achieving a PGA of "clear" or "almost clear" responses at any time during a multiple course of IM treatment with AMEVIVE (alefacept).

Replace the paragraph beginning at page 6, line 13 with:

A "multiple course of treatment" means at least three cycles of treatment. The cycles within a multiple course of treatment can be identical but they need not be identical, e.g., they may be different in dosing strategy during the administration period; or in duration of either the IA, length of administration period, rest period, or both. For example, a multiple course of treatment may include (a) a first cycle consisting of 12 weeks of once-weekly administration of AMEVIVE (alefacept) followed by 12 weeks of rest, followed by (b) a second cycle consisting of 12 weeks of once-weekly administration of AMEVIVE (alefacept) followed by a rest period of one year during which the agent has a substantial remittive effect on the patient, followed by (c) a third cycle consisting of 10 weeks of semi-weekly administration of

the therapeutic agent followed by two years of rest, followed optionally by (d) successive cycles, e.g., additional fourth, fifth, sixth, seventh, eighth cycles or more.

Replace the paragraph beginning at page 8, line 16 with:

AMEVIVE (alefacept) is a fusion protein that includes the first extracellular domain of human LFA-3 (CD58) fused to an Fc portion of human IgG1. In particular, AMEVIVE (alefacept) includes the amino terminal 92 amino acids of mature LFA-3, the C-terminal 10 amino acids of a human IgG1 hinge region containing the two cysteine residues thought to participate in interchain disulfide bonding, and a substantial part of the C.sub.H2 and C.sub.H3 regions of a human IgG1 heavy chain constant domain (e.g., SEQ ID NO:8). The protein is a glycosylated, disulfide linked dimer with a molecular weight of about 112 kD under PAGE nonreducing conditions. The constant region of AMEVIVE (alefacept) has C-terminal variability that corresponds to a splice variant form of the full length fusion polypeptide.

Replace the paragraph beginning at page 8, line 26 with:

A plasmid, pSAB152, encoding AMEVIVE (alefacept) is deposited with American Type Culture Collection, Rockville, Md., under the accession number ATCC 68720.

Replace the paragraph beginning at page 8, line 28 with:

pMDR(92)Ig-3 is an example of an expression vector that can be used to produce AMEVIVE (alefacept). pMDR(92)Ig-3 includes the following elements: (a) A segment of pBR322 containing the ColE1 origin and beta lactamase expression cassette (GenBank Accession No. J01749); (b) DHFR expression cassette consisting of: SV40 early promoter with the enhancer deleted (a portion of GenBank Accession No. J02400), murine DHFR cDNA (GenBank Accession No. L26316), SV40 poly A site and small t intron (portions of GenBank Accession No. J02400), and human gastrin transcription terminator sequence, 3'UTR (Sato et al. (1986) Mol Cell Biol 6:1032-1043); (c) an AMEVIVE (alefacept) expression cassette including, preferably in the following order: The SV40 early promoter/enhancer (GenBank Accession No. J02400), Adenovirus Major Late Promoter and tripartite leader, including a splice donor and intron sequence (a portion of GenBank Accession No. J01917), murine Ig heavy chain variable region intron sequence and splice

acceptor (Kaufman and Sharp (1982) Mol Cell Biol. 2: 1304-1319, (optionally) cloning linkers, the first 92 amino acids of LFA-3 gene as isolated from a human tonsil cDNA library, fused in frame to a nucleic acid encoding the hinge CH2 and CH3 regions of a human IgG1 gene as isolated from a human fibroblastic genomic DNA library, cloning linkers (optionally), MIS 3' UT region including poly A site (GenBank Accession No. K03474), and SV40 polyA site and small t intron (GenBank Accession No. J02400); and a segment of pBR327 (GenBank Accession No. L08856).

Replace the paragraph beginning at page 9, line 15 with:

Host cell lines that can be used to produce AMEVIVE (alefacept) can be derived from CHO-DUkX-B1 cells. In one embodiment, a DHFR(-) mutant of this cell line can be transfected with the vector pMDR(92)Ig-3, and DHFR(+) transformants can be cultured in selective medium (e.g., containing 25 nM of methotrexate (MTX)). Positive transformants can be subjected to increasing concentrations of MTX (e.g., 50 nM), and colonies producing high levels of AMEVIVE (alefacept) can then be selected.

Replace the paragraph beginning at page 9, line 21 with:

Production of AMEVIVE (alefacept) can be carried out as follows: CHO host cells are thawed, scaled up to a culture of 2000 L, maintained in culture for 6-7 days with pH control and nutrient feed (at 48 hrs., 96 hrs., and 120 hrs.), after which conditioned medium is harvested through microfiltration. MTX is preferably present in the culture medium. AMEVIVE (alefacept) can be recovered from the conditioned medium by carrying out the following steps: (i) Protein A chromatography, (ii) ceramic hydroxyapatite chromatography, (iii) viral inactivation at low pH, (iv) hydrophobic interaction chromatography, (v) followed by concentration, diafiltration, viral filtration, and a second concentration step which yields fusion product.

Replace the paragraph beginning at page 9, line 30 with:

Another way of producing AMEVIVE (alefacept) for use in the methods of this invention is described in co-pending, commonly assigned U.S. patent application Ser. No. 07/770,967. Generally, conditioned culture medium of COS7 or CHO cells transfected with pSAB152 was concentrated using an AMICON S1Y30 spiral cartridge system (AMICON,

Danvers, Mass.) and subjected to Protein A-Sepharose 4B (Sigma, St. Louis, Mo.) chromatography. The bound proteins were eluted and subjected to Superose-12 (Pharmacia/LKB, Piscataway, N.J.) gel filtration chromatography.

Replace the paragraph beginning at page 10, line 4 with:

Superose-12 fractions containing AMEVIVE (alefacept) with the least amount of contaminating proteins, as determined on SDS-PAGE gels and by Western blot analysis, (see, e.g., Towbin et al., Proc. Natl. Acad. Sci. USA, 74, pp. 4350-54 (1979); Antibodies: A Laboratory Manual, pp. 474-510 (Cold Spring Harbor Laboratory (1988)), were pooled and concentrated in a YM30 Centricon (AMICON). AMEVIVE (alefacept) was detected on Western blots using a rabbit anti-LFA-3 polyclonal antiserum, followed by detectably labeled goat anti-rabbit IgG. The purified AMEVIVE (alefacept) of COS7 or CHO cells was a dimer of two monomeric LFA-3-Ig fusion proteins, connected by disulfide bonds.

Replace the paragraph beginning at page 10, line 13 with:

LFA-3-Ig fusion activity can be tested using the following bioassays: (1) a CD32/64 (Fc gamma R1/R1) U937 cell bridging assay, and (2) a CD16 (Fc gamma RIII) Jurkat cell bridging assay. Both assays test the ability of AMEVIVE (alefacept) to bridge CHO cells displaying cell surface CD2 to cells expressing Fc-gamma receptors. The latter assay, assay (2), involves culturing adherent CH0--CD2 cells to form a monolayer in 96-well plates; adding AMEVIVE (alefacept) controls and samples; adding fluorescently labeled Jurkat-CD16(+); and measuring fluorescence intensity.

Replace the paragraph beginning at page 30, line 17 with:

The agent, e.g., CD2-binding LFA-3 polypeptide (e.g., AMEVIVE (alefacept)) is also preferably administered in a composition including a pharmaceutically acceptable carrier. By "pharmaceutically acceptable carrier" is meant a carrier that does not cause an allergic reaction or other untoward effect in patients to whom it is administered.

Replace the paragraph beginning at page 32, line 17 with:

AMEVIVE (alefacept) 7.5 mg was administered by intravenous (IV) bolus injection.

Replace the paragraph beginning at page 32, line 21 with:

Eligibility for a subsequent cycle was based on the aforementioned criteria and, in addition: patients must have received .gtoreq.8 doses of AMEVIVE (alefacept) during the 12-week treatment period of the previous cycle and for cycle C and subsequent cycles, lymphocyte counts were required to be .gtoreq.75% of the count recorded at the screening visit of the study.

Replace the paragraph beginning at page 32, line 26 with:

Within any given cycle, if patients had CD4+ T-cell counts <300 but >200 cells/mm.sup.3, the dose of AMEVIVE (alefacept) was reduced by 50% (3.75 mg). If CD4+ T-cell counts were <200 cells/mm.sup.3, the scheduled dose was withheld. If CD4+ T-cell counts were <200 cells/mm.sup.3 for 4 consecutive visits, AMEVIVE (alefacept) was permanently withheld. The AMEVIVE (alefacept) dose was withheld for 2 weeks when evidence of a clinically significant infection was seen.

Replace the paragraph beginning at page 33, line 15 with:

At the time of this analysis, patients have received repeated cycles of therapy with AMEVIVE (alefacept) over 4.5 years. In this study, 175 patients have received .gtoreq.1 cycle of AMEVIVE (alefacept); 126 received .gtoreq.2 cycles; 96 received .gtoreq.3 cycles; and 71 received .gtoreq.4 cycles. Some patients have received up to 9 cycles of AMEVIVE (alefacept) as a result of exposure to AMEVIVE (alefacept) in prior phase 2 studies.

Replace the paragraph beginning at page 33, line 27 with:

For cycles A-D, the incremental benefit and repeat response of additional cycles of therapy with AMEVIVE (alefacept) are shown in FIG. 3. For cycle A responders (i.e., patients who achieved PASI 50 in cycle A) who received additional cycles of AMEVIVE (alefacept), the proportions of patients who achieved PASI 50 increased with each subsequent cycle. In general, patients continued to respond to repeat treatment with AMEVIVE

(alefacept) with no evidence of tachyphylaxis. Of those who achieved PASI 50 in a given cycle, 75% to 90% of patients achieve PASI 50 in subsequent cycles (i.e., repeat response).

Replace the paragraph beginning at page 34, line 4 with:

The incidence of adverse events, in general, did not vary considerably across the cycles. The overall safety profile of AMEVIVE (alefacept) following administration of multiple cycles (a multiple course of treatment) is similar to that reported in phase 3 studies. The incidence of serious adverse events was 7% or less in any cycle, and the spectrum of serious adverse events was similar to previous phase 2 and 3 studies.

Replace the paragraph beginning at page 34, line 13 with:

In the phase 3 studies, the remittive action of AMEVIVE (alefacept) was demonstrated, with patients maintaining PASI 50 responses for a median of 7 months. In this example, some patients have been followed for prolonged periods after successful treatment cycles. FIG. 4 shows the maximum length of response time in 4 such patients. The response to therapy with AMEVIVE (alefacept) has been maintained for 18-24 months in some patients.

Replace the paragraph beginning at page 34, line 20 with:

Across multiple cycles of treatment with AMEVIVE (alefacept), decreases in lymphocyte counts were consistent. The decreases in lymphocyte counts observed with each cycle were not cumulative.

Replace the paragraph beginning at page 34, line 23 with:

Mean CD4+ T-cell counts remained above the LLN for all cycles and did not decrease with multiple-course exposure to AMEVIVE (alefacept) (FIG. 5).

Replace the paragraph beginning at page 34, line 25 with:

In sum, this study shows that a multiple course of treatment (3 cycles of treatment or more) provides more significant results than a single course of therapy, with no apparent

additional risk of side effects. Multiple cycles of AMEVIVE (alefacept) were well-tolerated by patients, and the incidence of adverse events did not vary considerably across the cycles.

Replace the paragraph beginning at page 34, line 31 with:

Example 2: Multi-course treatment of psoriasis with AMEVIVE (alefacept)

Replace the paragraph beginning at page 34, line 32 with:

This example examined the clinical response to a second cycle of treatment with AMEVIVE (alefacept) in psoriasis patients who failed to achieve a $\geq$ 50% reduction in Psoriasis Area and Severity Index (PASI 50) or a $\geq$ 25% reduction (PASI 25) during a first cycle of treatment with AMEVIVE (alefacept), as well as the efficacy of multiple cycles of therapy.

Replace the paragraph beginning at page 35, line 4 with:

Patients were $\geq$ 16 years old and had chronic plaque psoriasis for $\geq$ 12 months that involved $\geq$ 10% of body surface area. CD4+ T-cell counts were required to be above the lower limit of normal (LLN). Treatment with phototherapy, systemic retinoids, systemic corticosteroids, systemic fumarates, immunosuppressants (methotrexate, cyclosporine, azathioprine, and thioguanine), and high-potency topical corticosteroids was prohibited within 4 weeks before treatment with AMEVIVE (alefacept) and throughout the studies. Use of moderate-potency topical corticosteroids, topical retinoids, coal tar, keratolytics, and vitamin D analogues was prohibited within 2 weeks of treatment with AMEVIVE (alefacept) and throughout the studies, except on the scalp, palms, groin, and soles. To be eligible for enrollment in the extension studies, patients were required to have received $\geq$ 8 doses of AMEVIVE (alefacept) and completed the final follow-up visit of the previous cycle of therapy. Patients were excluded from the extension studies if they enrolled in any other investigational studies of drug or nondrug therapy or initiated alternative systemic psoriasis treatments, phototherapy, or other disallowed therapies prior to week 8 of the previous cycle.

Replace the paragraph beginning at page 35, line 20 with:

The phase 3 studies were multicenter, randomized, double-blind, and placebo-controlled (Krueger et al., J. Am. Acad. Dermatol. 47:821-833, 2002; Lebwohl et al., Arch.

Dermatol. 139:719-727, 2003). In the phase 3 study of intravenous (IV) treatment with AMEVIVE (alefacept), patients received two cycles of treatment, where each cycle consisted of (i) a 12 week administration period of either once weekly AMEVIVE (alefacept) (7.5 mg) or placebo, and (ii) a 12 week follow-up (rest period). In the phase 3 study of intramuscular (IM) treatment with AMEVIVE (alefacept), patients received a single cycle of treatment that consisted of a 12 week administration period of either AMEVIVE (alefacept) (10 mg or 15 mg) or placebo once weekly, followed by 12 weeks of observation (rest period).

Replace the paragraph beginning at page 35, line 30 with:

In the multiple course therapy studies, patients who received additional cycles of treatment with AMEVIVE (alefacept) (same dosage regimen) were those whose disease had progressed to require systemic therapy or phototherapy, as determined by the investigator, and had circulating CD4+ T-cell counts at or above the LLN (Gordon et al., J. Drugs Dermatol. 2:624-628, 2003).

Replace the paragraph beginning at page 36, line 11 with:

Data from the 2-cycle phase 3 study of IV treatment with AMEVIVE (alefacept) were used to determine the efficacy of a second cycle of treatment with AMEVIVE (alefacept) in two groups of patients: (a) those who failed to achieve PASI 50 in the first cycle and (b) those who failed to achieve PASI 25 in the first cycle. Proportions of patients who failed to achieve PASI 50 and PASI 25 during cycle 1 of treatment with AMEVIVE (alefacept) who achieved PASI 50 or PASI reductions of $\geq$ 75% (PASI 75) at any time during a second cycle of treatment were determined. Odds ratios and corresponding 95% confidence intervals (CIs) were calculated to compare response rates between patients who received a second cycle of treatment with AMEVIVE (alefacept) and those who received placebo. Proportions of patients who achieved PASI 50, PASI 75, and PGA of "clear" or "almost clear" at any time during each of the IV treatment cycles, and the proportion of patients who achieved a PGA of "clear" or "almost clear" at any time during each of the IM treatment cycles were also determined.

Replace the paragraph beginning at page 36, line 25 with:

[0157] Patients had a mean age of ~ 45 years, and ~ 70% were male. The median duration of psoriasis was ~ 19 years, and the median body surface area involvement was ~ 22%. The number of patients receiving each cycle of IV and IM treatment with AMEVIVE (alefacept) is summarized in Table 1.

Replace the table beginning at page 37, line 1 with:

	Treatment Cycle				
	1	**2**	**3**	**4**	**5**
IV AMEVIVE (alefacept)	521	327	217	158	39
IM AMEVIVE (alefacept)	457	320	156	100	50

TABLE 1: Number of patients receiving multiple cycles of AMEVIVE (alefacept).

Replace the paragraph beginning at page 37, line 9 with:

PASI improvement was observed during a second cycle of IV treatment with AMEVIVE (alefacept) in 93% of patients who failed to achieve PASI 50 during the first cycle and 89% of patients who failed to achieve PASI 25 during the first cycle. Treatment with AMEVIVE (alefacept) in the second cycle resulted in significantly greater proportions of patients achieving PASI 50 and PASI 75 than placebo treatment (Table 2). 19% of patients who failed to achieve PASI 50 during the initial cycle of treatment with AMEVIVE (alefacept) achieved PASI 75 during the second cycle and 53% achieved PASI 50.14% of patients who failed to achieve PASI 25 during the initial cycle of treatment with AMEVIVE (alefacept) achieved PASI 75 during the second cycle and 47% achieved PASI 50 (Table 2). Odds ratios showed that patients who failed to achieve PASI 50 or PASI 25 in cycle 1 were 2 to 3 times more likely to achieve PASI 50 or PASI 75 in cycle 2 compared with patients who did not receive another cycle (Table 2).

Replace the table beginning at page 38, line 1 with:

	Treatment		
	AMEVIVE-AMEVIVE (alefacept)	AMEVIVE-(alefacept) PLACEBO	Odds ratio (95% CI)
Patients who did not achieve PASI 50 in first AMEVIVE (alefacept) cycle			
N	97	86	
PASI 75, n (%)	18 (18.6)	7 (8.1)	2.57 (1.02-6.50)
PASI 50, n (%)	51 (52.6)	28 (32.6)	2.30 (1.26-4.19)
Any PASI improvement, n (%)	90 (92.8)	74 (86.0)	2.08 (0.78-5.56)
Patients who did not achieve PASI 25 in first AMEVIVE (alefacept) cycle			
N	66	46	
PASI 75, n (%)	9 (13.6)	3 (6.5)	2.26 (0.58-8.86)
PASI 50, n (%)	31 (47.0)	11 (23.9)	2.82 (1.23-6.48)
Any PASI improvement, n (%)	59 (89.4)	38 (82.6)	1.77 (0.59-5.29)

TABLE 2: PASI improvement at any time during a second cycle of AMEVIVE (alefacept) in patients who failed to achieve PASI 50 or PASI 25 during the first cycle.

Replace the paragraph beginning at page 38, line 9 with:

Patients who received multiple cycles of IV treatment with AMEVIVE (alefacept) showed incremental improvement in PASI during each subsequent treatment cycle. The proportion of patients achieving PASI 75 increased from 29% during cycle 1 to a maximum of 54% during cycle 5 (FIG. 6A). Similarly, the proportion of patients achieving PASI 50 increased from 56% during cycle 1 to a maximum of 74% during cycle 5 (FIG. 6B).

Replace the paragraph beginning at page 38, line 15 with:

PGA results further support the incremental clinical improvement in psoriasis observed with multiple cycles of treatment with AMEVIVE (alefacept). 23% of patients had a PGA of "clear" or "almost clear" during cycle 1 of IV treatment with AMEVIVE (alefacept). During cycle 5, 44% of patients achieved this level of response (FIG. 7A). For IM treatment with AMEVIVE (alefacept), PGA "clear"/"almost clear" response rates increased from 21% during cycle 1 to a maximum of 41% during cycle 4 (FIG. 7B).

Replace the paragraph beginning at page 38, line 21 with:

In sum, incremental clinical improvement is seen following successive cycles of treatment with AMEVIVE (alefacept), indicating its efficacy for the long-term treatment of patients with chronic plaque psoriasis. Multiple course therapy data show that patient response to additional treatment with AMEVIVE (alefacept) is incrementally beneficial regardless of response to the initial treatment.